

microns), and a relatively high porosity (i.e. loose bulk density of 0.2-0.4g/cc). The examples of the present application demonstrate that these microcrystalline cellulose granules provide an enhanced cushioning effect compared to similar, commercially available microcrystalline cellulose granules whereby these granules of microcrystalline cellulose can be employed to protect controlled-release particles contained in pharmaceutical formulations during tableting operations.

Claims 1-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,123,964 (Asgharnejad et al.) in view of U.S. Patent No. 5,725,886 (Erkoboni et al.). This rejection is respectfully traversed and reconsideration is requested for the reasons, which follow.

The Examiner takes the position that,

"The Asgharnejad et al patent discloses a process comprising the steps that involves (1) forming a powder blend of the active ingredient with a binder/diluent, a first diluent, a second diluent, and a disintegrant, using a mixer; (2) wet granulating the powder blend by adding a solution of ethanol/water to the powder blend; (3) drying the granules to remove the ethanol/water with heated air in a fluidized bed dryer or tray dryer (see column 2, line 63 to column 3, line 6)."

The applicant respectfully submits that the Official Action does not set forth a *prima facie* case of obviousness in support of the rejection under 35 U.S.C. § 103(a). According to M.P.E.P. § 2143,

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. [Citations omitted]

Claims 1-13, as amended, require a two-step drying process that is neither taught nor suggested in Asgharnejad et al. In the first step of this two-step drying process, substantially all of the polar organic solvent is removed from the microcrystalline cellulose granules without removing a substantial

portion of the water from the granules. In the second step, after substantially all of the polar organic solvent has been removed, a substantial portion of the water is removed. This two-step drying process provides a novel porous microcrystalline cellulose product that exhibits enhanced cushioning properties for cushioning controlled-release particles during tableting, as is demonstrated in the examples of the present application.

Asgharnejad et al. does not disclose a two step drying process, but instead discloses a single step of drying to remove the ethanol/water with heated air in a fluid bed dryer or tray dryer for 10 minutes to 24 hours. Thus, the process of Asgharnejad et al. is distinguishable from the process of claims 1-13 of the present application, as amended, for at least this reason. Asgharnejad et al. also does not teach or suggest carrying out the drying step in two stages as in the present invention nor does Asgharnejad et al. give a skilled person any reason to believe that a two step drying process would be beneficial. Erkoboni et al. also does not disclose the use of the two-step drying process of the present invention and thus does not cure the deficiency of Asgharnejad et al.

In the Final Rejection, the Examiner first takes the position that,

“the instant claims do not set forth a critical temperature and critical time for carrying out the drying process that is substantially different from the temperature and time used for the drying process that is disclosed in the Asgharnejad et al. patent.”

However, this is not correct since the present claims require, in functional terms, use of a critical temperature and critical time that results in a first step of drying to remove substantially all of the polar organic solvent without removing a substantial portion of the water, and then a subsequent step of drying to remove the water. This is clearly different from Asgharnejad et al. which conducts the entire drying process as a single step and does not teach, suggest or mention the possibility of changing the drying conditions during the drying step.

In fact, the Examples of the present application demonstrate that the process of the present invention gives significant, unexpected improvements in the properties of the product dried using a two-step process, as compared to products dried using a one step drying process in accordance with Asgharnejad et al. Examples 1-2 of the present invention uses a two-step drying process, as claimed (See page 11, lines 10-14 and page 12, lines 6-9 of the application). Comparative Examples B-C found on pages 12-23 of the original application employ a one-step drying process in accordance with Asgharnejad et al. (See page 13, line 6 of the application). Examples 1-2, using the two-step drying process as claimed, each produced tablets with acceptable cushioning properties, whereas Comparative Examples B-C, using a one-step drying process as disclosed in Asgharnejad et al., produced tablets that were too dense to provide adequate cushioning properties. These examples tend to show that there is, in fact, a significant, unexpected difference between products made by the claimed drying process of the present invention, as compared to products made using a one step drying process as disclosed in Asgharnejad et al. Therefore, it is considered that the applicant has, in fact, clearly distinguished the drying process of the present invention over the drying process of Asgharnejad et al.

The Examiner also took the position that it is well known in the art that ethanol will evaporate before water in a drying process to remove a solvent comprising ethanol and water. This is incorrect since it is well known that ethanol and water form an azeotrope that cannot be separated by distillation. Thus, a mixture of water and ethanol will always evaporate together. The present inventors were the first, however, to appreciate that selection of a two-step drying process in order to minimize the evaporation of water along with the ethanol, would produce a material having improved cushioning properties, as compared to materials made using the one step drying process, as shown by the Examples discussed above.

Thus, in summary, the rejection over Asgharnejad et al. in view of Erkoboni should be withdrawn for the following reasons:

1. The Examiner has failed to make out a *prima facie* case of obviousness since neither of the cited references teaches or suggests the element of the present claims which requires a two-step drying process.
2. Even if a *prima facie* case of obviousness were made by the Examiner, Examples 1-2 and Comparative Examples B-C tend to demonstrate that the two-step drying process of the present invention provides a significant, unexpected benefit over the one-step drying process of Asgharnejad et al. which renders the invention patentable.

Accordingly, favorable consideration and withdrawal of the rejection are requested.

Claims 14-15 and 18-26 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over McTeigue et al. (U.S. Patent No. 6,149,943). This rejection is respectfully traversed and reconsideration is requested for the reasons which follow.

The applicant respectfully submits that the Official Action does not set forth a *prima facie* case of obviousness in support of the rejection under 35 U.S.C. § 103(a). According to M.P.E.P. § 2143,

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. [Citations omitted]

There are two important differences between the present invention, as claimed in claim 14, and the disclosure of McTeigue et al. These differences are as follows:

1. Claim 14 requires that the microcrystalline cellulose have a mean or median particle size of at least 250 microns, whereas McTeigue et al. teaches that the microcrystalline cellulose should have an median particle size of 160-220 microns, and
2. Claim 14 requires that the microcrystalline cellulose have a loose bulk density of from about 0.2 g/cc to about 0.4 g/cc, whereas McTeigue et al. teaches that the microcrystalline cellulose should have a tapped bulk density of from 0.40-0.45 g/cc.

Thus, to arrive at the present invention from McTeigue et al., the person of ordinary skill in the art would have to:

1. Start with a mean particle size of 160-220 microns as disclosed in McTeigue et al.,
2. Somehow arrive at a mean particle size of greater than 250 microns even though McTeigue et al. contains no teachings relating to the mean particle size other than that the mean particle size should be 160-220 microns,
3. determine that loose bulk density is an important characteristic since it is not mentioned in McTeigue et al., and
4. Somehow arrive at a loose bulk density of 0.25 to 0.40 g/cc even though McTeigue et al. contains no teachings relating to the loose bulk density of the material.

In view of the foregoing, the Examiner has not made out a *prima facie* case of obviousness, since each of the following are missing from what is required to make out a *prima facie* case:

1. at least two elements of claim 14 are not disclosed in McTeigue et al., namely a mean particle size of at least 250 microns, and a loose bulk density of from about 0.25 to about 0.40 g/cc,

2. McTeigue et al. contains no teaching to lead a skilled person to modify the mean particle size of 160-220 microns disclosed in McTeigue et al. to arrive at the mean particle size of claim 14,
3. McTeigue et al. contains no teaching to lead a skilled person to arrive at the loose bulk density of claim 14,
4. McTeigue et al. contains no teaching to lead a skilled person to expect that use of a mean particle size of greater than 250 microns would provide any benefit whatsoever, and
5. McTeigue et al. contains no teaching to lead a skilled person to expect that use of a loose bulk density of 0.25-0.40 g/cc would provide any benefit whatsoever.

The Examiner took the position that the disclosure of a median particle size of up to 220 microns with a particle size standard deviation of about 75 to about 200 microns embraces the microcrystalline cellulose granules of the instant claims. This is not correct. The standard deviation of about 75 to about 200 microns disclosed in McTeigue et al. only indicates that the particle size of individual particles may vary within a range of about 75 to 200 microns from the largest particle to the smallest particle. This indicates that the particle size distribution of McTeigue et al is narrow (See col. 2, lines 44-49), but tells the skilled person nothing about the median particle size.

Thus, McTeigue et al. contains a clear teaching that the mean or median particle size should be between 160 and 220 microns, and there is no motivation to change this in view of the disclosure of McTeigue et al. Thus, a skilled person following the teachings of McTeigue et al. would use a mean particle size of 160-220 microns and not greater than 250 microns as required by the present claims. The standard deviation in particle size does not change this since this information only pertains to the particle size distribution and does not provide any reason to operate with a mean particle size outside the disclosed range of McTeigue et al. of 160-220 microns.

With respect to the bulk density, loose bulk density and tapped bulk density are different parameters which are measured using different measurement methods. The Examiner has not shown that there is any relationship between loose bulk density and tapped bulk density and thus there is no way to determine from McTeigue et al. what the loose bulk density of the materials is. The only information available that is potentially relevant to this point is that the composition of Example 2 of the present application is said to have a tapped bulk density of 0.3247 g/cc. This example is thus clearly outside the range disclosed in McTeigue et al. of a tapped bulk density of 0.40-0.45 g/cc. Thus, the skilled person reading McTeigue et al. cannot determine that the particles should have a **loose bulk density** of 0.25-0.40 g/cc as claimed and, in view of Example 2, the skilled person would be led to conclude that the particles of the present invention do not fall within the range disclosed in McTeigue et al. since the particles of Example 2 of the present application have a tapped bulk density that is far below the range disclosed in McTeigue et al.

All of claims 15-16 and 18-26 contain the foregoing limitations or more restrictive ranges and thus are considered patentable for at least these same reasons. Accordingly, favorable consideration and withdrawal of the rejection under 35 U.S.C. §103(a) over McTeigue et al. is requested.

Claim 17 has been rejected under 35 U.S.C. §103(a) as being unpatentable over McTeigue et al. as applied to claims 14-16 and 18-26 above, and further in view of Kumar (U.S. Patent No. 6,117,451). This rejection is respectfully traversed and reconsideration is requested for the reasons, which follow.

Kumar discloses microcrystalline cellulose that has a particle size range of 150-220 microns and a density range of 0.20-0.45 g/ml (col. 9, lines 21-23). Claim 17 differs from Kumar in that claim 17, requires microcrystalline cellulose granules having median particle sizes greater than 250 microns and because claim 17 specifies a particular **loose bulk density** whereas Kumar only mentions a density range but does not specify that this is a loose bulk density.

Thus, a combination of McTeigue et al. and Kumar still does not make out a case of *prima facie* obviousness since the following elements of a case of *prima facie* obviousness are missing from a combination of McTeigue et al. and Kumar:

1. at least two elements of claim 14 are not disclosed in McTeigue et al., namely a mean particle size of at least 250 microns, and a loose bulk density of from about 0.25 to about 0.40 g/cc,
2. McTeigue et al. contains no teaching to lead a skilled person to modify the mean particle size of 160-220 microns disclosed in McTeigue et al. to arrive at the mean particle size of claim 14 and Kumar teaches that all particles should be in the range of 150-200 microns (see col. 9, lines 21-23 of Kumar),
3. Neither McTeigue et al. nor Kumar contains no teaching to lead a skilled person to arrive at the loose bulk density of claim 14 and Kumar does not even mention loose bulk density,
4. Neither McTeigue et al. nor Kumar contains no teaching to lead a skilled person to expect that use of a mean particle size of greater than 250 microns would provide any benefit whatsoever, and
5. Neither McTeigue et al. nor Kumar contains a teaching to lead a skilled person to expect that use of a loose bulk density of 0.25-0.40 g/cc would provide any benefit whatsoever.

The Examiner also takes the position that, "The Kumar patent shows that the claimed bulk density for microcrystalline cellulose is well known in the art by disclosing a density range of 0.20 to 0.45 g/ml for the microcrystalline cellulose thereof." This conclusion is not correct. First, the Kumar patent does not teach or suggest that the particular density range is "well-known in the art." Rather, Kumar teaches that some forms of microcrystalline cellulose may have a density range of 0.20-0.45

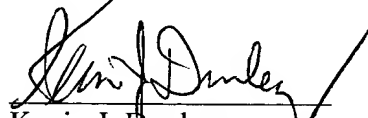
g/ml. However, these forms of microcrystalline cellulose also have a particle size of 150-200 microns. The present claims require microcrystalline cellulose having a mean particle size of at least 250 microns. Thus, the microcrystalline cellulose described in Kumar is clearly a different product than the microcrystalline cellulose of the present invention. Thus a skilled person, reading Kumar, would not know what the density of the microcrystalline cellulose of the present invention would be since Kumar does not even contemplate the existence of microcrystalline cellulose having a mean particle size greater than 250 microns, as claimed.

Note also that Kumar only states that the density should be from 0.20-0.45 g/ml., but does not specify that this is a loose bulk density. Thus, this density could be a tapped bulk density or even some other density measurement but it is certainly not clear that this refers to a loose bulk density.

Finally, even if the skilled person were to modify McTeigue et al. to use a microcrystalline cellulose as disclosed in Kumar, both McTeigue et al. and Kumar teach that the particle size of the microcrystalline cellulose should be significantly smaller than the median particle size of 250 microns as presently claimed and thus the modification of only the loose bulk density, as suggested by the Examiner, is not enough to arrive at the present invention as claimed in claim 17. In fact, a skilled person desiring to achieve the inherent binding and superior tableting flow properties of Kumar would be motivated to use a microcrystalline cellulose having a particle size of 150-200 microns as disclosed in Kumar, a product that is clearly outside the range of claim 17. Thus, the skilled person would not arrive at the median particle size claimed in the present application. Accordingly, favorable consideration and withdrawal of the rejection of claim 17 over McTeigue et al. in view of Kumar is requested.

Favorable consideration and issuance of a notice of allowance are solicited.

Respectfully submitted,



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